Letters to the Editor . . .

MILK-BORNE CARCINOGENIC VIRUS

In 1936 it was shown by Bittner[1] that the apparently spontaneous mammary cancer in certain strains of mice is due to an "influence" or "incitor," transferred by nursing from the mother to the new-born young. Young born of the carcinophilic strain and foster-fed by mothers free from this apparently hereditary taint seldom if ever develop spontaneous breast cancer in late life. Young born from cancer-free strains and foster-fed by carcinophilic mothers often developed lethal breast cancer. It was afterwards shown that the same "incitor" may be demonstrated in either spontaneous or transplanted mammary cancer of mice[2] or in apparently normal lactating mammary tissues[3] of certain strains.

The active agent is present in cell-free filtrates from mammary carcinoma.[4] Tests were made on 4 or 5 week old females which had parents that did not transfer the influence in their milk but which had the inherited susceptibility for spontaneous mammary cancer. These young mice were inoculated intraperitoneally with Berkefeld filtrates from carcinoma tissues. In a typical group of 10 mice inoculated with such filtrates, 8 died and in a second group of 22 mice similarly inoculated, 12 died of spontaneous mammary cancer by the end of 12 months. The incidence of mammary cancer in several hundred uninoculated controls was less than 1 per cent.

These data suggest that the carcinogenic "influence" is a filtrable virus. If so, the "influence" presumably multiplies or is multiplied in symbiosis with mammary tissues. To test this possibility, 10 serial transplants of carcinoma tissue were made in mice that did not themselves carry the active milk agent. Berkefeld filtrates from the 10th serial passage caused the development of lethal mammary cancer in 8 out of 12 injected mice. There is thus evidence of the continuous production of the active agent within the transplanted tumor cells. Attempts to propagate the "influence" in embryonated hens eggs, thus far have not been very convincing, even though the milk agent survives for 12 days in the yolk sac in the absence of living mouse cells.

In order to obtain further evidence in support of the virus theory, Green[5] and his associates of the University of Minnesota studied the antigenic properties of the mouse-tumor agent. To do this, high-speed centrifugates from mouse mammary carcinoma filtrates were repeatedly injected into rabbits and white rats, both spontaneous mammary tumors and transplant tumors being used in making the filtrates. Control injections were made with filtrates from normal mouse tissues. Seven to ten days after the 5th injection serums were drawn from the injected animals, and tested for their possible virucidal action on the mouse-tumor agent.

To do this, centrifugate equivalents of 0.2 g. tumor tissue were suspended in 0.5 cc. saline solution and mixed with 0.18 cc. antiserum. After 2 hours standing at room temperature, 24 4-week old mice were injected with each mixture. Of 48 control mice injected with virus alone or with a mixture of virus and an antiserum against normal mouse tissues, 39 or 80 per cent developed breast tumors by the end of 13.5 months. Of 48 mice injected with a mixture of virus and specific antiserum (anti-milk "influence"), not a single case of breast tumor developed during the same period of time.

These findings confirm the earlier hypothesis that the milk agent is of exogenous origin. Whether or not the specific virucidal antiserum would be therapeutically effective in mice already infected with the milk-borne virus has not yet been tested.

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PROTEIN-REPLETION THERAPY

In 1942 it was shown by Cannon[1] of the Department of Pathology, University of Chicago, that antibody formation is largely a function of protein reserves. Rabbits whose protein reserves had been reduced by plasmapheresis or prolonged low protein diets usually produced agglutinins of but one-fifth the titer of agglutinins produced by well-fed controls.

His implied theory of acquired immunity was of particular interest at that time due to its application to the epidemiology of infectious diseases under wartime conditions. Cannon[2] subsequently found that there is a positive correlation between protein deficiency and surgical infection. It therefore became of practical clinical interest to determine how promptly and effectively protein depletion can be corrected by dietary measures.

To test this[3] groups of adult white rats were placed on a protein depletion diet. The diet usually contained less than 2 per cent protein, with compensatory increases in non-protein factors so as not to reduce caloric intake. Vitamin intake was left constant. By the end of 83 to 191 days, there was 30 to 40 g. loss of body weight, and a 30 per cent reduction in hemoglobin and serum proteins. These depleted rats were then injected in the tail vein with washed sheep erythrocytes. They produced antiserums averaging 560 hemolytic units per cc. by the end of 6 days. As controls, normally fed rats were similarly injected. They produced antiserums averaging 560 hemolytic units per cc. by the end of 6 days. As controls, normally fed rats were similarly injected. They produced antiserums with an average hemolytic titer of about 8,000 units per cc. by the end of the same period, or 14 times the antibody titer of the depleted rats.

Protein-repletion tests were now made on other groups of depleted rats. To do this dehydrated beef, lacalbumin or proteinhydrolysate ("amigen") were added to the depletion diets in such a way as to increase the protein (or its equivalent) to about 20 per cent. There was practically no change in daily vitamins or caloric intake. Animals on these repletion diets made satisfactory weight recoveries (35-50 g. per rat) and serum protein regeneration (2.05 to 2.96 g. per cent) by the end of 7 days. During this 7-day recovery period, injection of washed sheep erythrocytes led to the production of antiserums of an average hemolytic titer of 3,830 units per cc. by the end of 6 days. This was nearly 7 times the average titer in depleted rats. A 2.6-fold improvement was seen after only 2 days protein-repletion feeding, increasing to

nearly a 10-fold increase by the end of 7 days therapeutic feeding.

Depression of specific antibody function by protein depletion is therefore reversible. Feeding with high-quality protein or its equivalent will therefore restore within about 7 days a depleted animal's ability to produce antibodies of relatively normal titer. These findings suggest that it is not only important in a rehabilitation program to feed severely undernourished persons rations high in calories and vitamins, but also rations containing an adequate amount of high-quality proteins or their equivalent, particularly when bacterial infection is preesnt or impending.

The exact mechanism whereby protein depletion depresses specific antibody production and protein repletion re-establishes it is still undetermined.

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BOOK REVIEWS

A BIBLIOGRAPHY OF INFANTILE PARALYSIS WITH SELECTED ABSTRACTS AND ANNOTATIONS —1789-1944. Prepared under direction of the National Foundation for Infantile Paralysis, Inc. Edited by Morris Fishbein, M.D., Editor, Journal of the American Medical Association; compiled by Ludvig Hektoen, M.D., Chief Editor, Archives of Pathology and Ella M. Salmonsen, Medical Reference Librarian, John Crerar Library, Chicago. Cloth. Pp. 672. Philadelphia, London, Montreal: J. B. Lippincott Company, 1946.

The last comprehensive survey of the literature on poliomyelitis was that of the Milbank International Committee published in 1932. During the 14 years that have since elapsed the many workers in that field have increasingly felt the need of another and more complete bibliography. The Milbank report consisted of a series of reviews of various phases of the subject and its bibliography contained only 830 of the more than 5,000 items which the present volume shows had been published up to that time. The latter contains over 8,400 references for the period ending with 1944, a striking witness to the tremendous interest which poliomyelitis has attracted in the medical profession and its ancillary services.

The arrangement of the present volume is admirable. The articles are consecutively numbered and listed by year, those within each year being given alphabetically. At the end of the volume is an index of authors followed by a subject index. The latter, while occupying 94 pages and extraordinarily detailed, is not absolutely complete. The important study of Rissler, for example, in which the first detailed histopathological study of acute poliomyelitis was presented, is not listed under Pathologic anatomy nor under Pathology, probably because of its undescriptive title. An occasional omission of this sort is, of course, humanly unavoidable. Brief but usually adequate abstracts of papers of more than ordinary interest are given.

Of special interest to Californians is the fact that the first case report from this state (of a patient from Eureka) appeared in 1874-75 in the Pacific Medical and Surgical Journal under the name of G. M. Kober. The first recorded epidemic here, that of 1901 consisting of 55 known cases, was reported by Alice M. Woods in 1903 in the *Occident Medical Times*. The epidemic of 1910 was still larger, necessitating the appointment of a committee for the Study of Anterior Poliomyelitis in San Francisco under the chairmanship of the late E. C. Fleischner; its report in the *California State Medical Journal* was published in 1911 and recorded 139 or more cases. It was not until this time or shortly thereafter that the disease was officially listed and systematically reported in public health reports. For this state as elsewhere it is impossible to obtain an accurate estimate of the prevalence of poliomyelitis in the nineteenth and early part of the twentieth century because reporting was casual and haphazard and the disease was classified with meningitis and other infections of the central nervous system. But the bibliography clearly indicates that the disease which during the last four decades has occurred in such large epidemics in the temperate zones began with sporadic cases and small outbreaks and took more than a century to reach its recent proportions.

The reviewer has not time nor space to discuss the many other interesting facts disclosed by the present volume, such as the development of our present knowledge of the pathology, epidemiology, clinical aspects, experimental research, and therapy, but they are covered with gratifying completeness and ease of reference. The medical world is deeply indebted to the National Foundation for Infantile Paralysis and to the labors of the editors of the bibliography for a notable addition to its armamentarium. Special commendation is due for the handsome format and conspicuously legible typeface of the volume.

PHYSICAL CHEMISTRY OF CELLS AND TISSUES. By Rudolf Hober, University of Pennsylvania School of Medicine, Philadelphia, Pa.; with the collaboration of David I. Hitchcock, Yale University School of Medicine, Laboratory of Physiology, New Haven, Conn.; J. B. Bateman, Mayo Clinic, Rochester, Minn.; David R. Goddard, University of Rochester, Biological Laboratories, Rochester, N. Y., and Wallace O. Fenn, University of Rochester, School of Medicine and Dentistry, Rochester, N. Y. Cloth. Price, $9.00. Pp. 676, illustrated. Philadelphia: The Blakiston Company, 1945.

As the title indicates, this book is for the experimental investigator of fundamentals of biological function, chiefly cells, including living and non-living models. This approach has been of unquestionable value in shedding light on the physico-chemical nature of living function, but the reader may sometimes wonder whether the devotees of this approach are making physiology the handmaid of physics and chemistry, for their sake, or whether the nature of living function is being explained in and for itself. Woodger has pointed out the serious limitation to, if not fallacy of, attempting to account for biological phenomena according to laws of physics and chemistry, and he gives many examples in his own book where these inanimate sciences fail conspicuously to elucidate striking and common every day phenomena. It would seem there is something "vital" (perhaps a poor term) or peculiar to the behavior of living tissues which must be taken into account for a better understanding of function than merely physics and chemistry. For instance, selectivity,